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Surface-Tension Replica-Exchange Molecular Dynamics Method for Efficient Conformational Sampling of Biological Membrane Systems
Takaharu Mori[1,2], Jaewoon Jung[3], Yuji Sugita[1,2].
[1]Theoretical Molecular Science Laboratory, RIKEN, Wako-shi, Saitama, Japan, [2]Quantitative Biology Center, RIKEN, Kobe-shi, Hyogo, Japan, [3]Advanced Institute for Computational Science, RIKEN, Kobe-shi, Hyogo, Japan.
Conformational sampling is fundamentally important for simulating complex bio-molecular systems. Generalized-ensemble algorithm, especially the temperature replica-exchange molecular dynamics method (REMD), is one of the widely used methods to explore structures of bio-molecules. Most temperature REMD simulations have focused on soluble proteins rather than membrane proteins or lipid bilayers, because explicit membranes do not keep their structural integrity at high temperature. Here, we propose a new generalized-ensemble algorithm for membrane systems, which we call the surface-tension REMD method. Each replica is simulated in the NPγT ensemble, where surface tensions in a pair of replicas are exchanged at certain intervals to enhance conformational sampling of the target membrane system. We tested our method on a fully hydrated DPPC lipid bilayer. During the simulation, a random walk in surface tension space is realized. Large-scale lateral deformation of DPPC membranes takes place in all of the replicas without collapse of the lipid bilayer structure. Our method could be applicable to a wide variety of biological membrane systems including mixed lipid bilayers and membrane-protein systems.

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What Happens for Sterol Dynamics When Cholesterol is Enzymatically Oxidized?
Moutusi Manna[1], Sini Mokkila[1], Matti Javanainen[1], Tomasz Rog[1], Maarit Neuvonen[2], Elina Ikonen[2,3], Ilpo Vattulainen[1,4].
[1]Department of Physics, Tampere University of Technology, Tampere, Finland, [2]Institute of Biomedicine, Anatomy, University of Helsinki, Helsinki, Finland, [3]Minerva Foundation Institute for Medical Research, Helsinki, Finland, [4]Memphys Center for Biomembrane Physics, University of Southern Denmark, Odense, Denmark.
Cholesterol is an essential component of the mammalian cell membrane. Thermal fluctuations of cholesterol from its equilibrium position, along the bilayer normal, have important consequences in its cellular trafficking. In this work, we have investigated the effect of replacing part of membrane cholesterol with one of its oxidative products, cholestenone (4-cholesten-3-one, a ketosterone that differs from cholesterol only in the hydroxyl headgroup and the position of double bond), on the transbilayer movement (flip-flop). In the same spirit, we have studied desorption of these sterols from a membrane towards the aqueous phase. The reason why we focus on cholestenone is that it is one of the most common products when cholesterol is being oxidized, thus serving as an example of cholesterol oxidation. The results from our atomistic molecular dynamics simulations show that replacing the hydroxyl group of cholesterol by the keto group found in cholestenone has a significant effect on inter-leaflet translocation of the sterol. To discuss the cause and consequences of the observed effects, we used umbrella (free energy) simulations to calculate the potential of mean force for flip-flop as well as for desorption of these two sterols from the membrane into the water phase. The results brought out that even seemingly tiny changes in sterol structure have considerable implications for sterol dynamics. As cholesterol oxidation is often used to deplete cholesterol in experimental conditions, our results highlight that it is essential to understand the membrane behavior of the introduced lipid species, in this case cholestenone.

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Development of Coarse-Grained Martini Model for Nucleic Acid Structures
Parisa Akhshi[1], Jaakko Uusitalo[2], Helgi Ingolfsson[2], Siewert-Jan Marrink[2], D. Peter Tieleman[1].
[1]University of Calgary, Calgary, AB, Canada, [2]University of Groningen, Groningen, Netherlands.
Molecular modeling has been extensively used to describe various properties of biological systems with all-atom detail. However, its application has been limited by the size of the system and accessible simulation times. During the past few years, the coarse-grained Martini model has been developed for biomolecular systems, allowing larger scale simulations not affordable by all atom models1. Despite significant progress in modeling biomolecules such as lipids and proteins, Martini has not been properly parameterized yet to describe nucleic acids. A reliable description of nucleic acids would enable studies of a range of important problems involving DNA, RNA, and their complexes with proteins and lipids. One example of the latter is lipid nanoparticles (LNPs). LNPs are effective delivery systems for transferring small interfering RNA (siRNA) into the cell, where they can induce silencing of a target gene2. Lipid-nucleic acid interactions and their energetics are important in the gene delivery step in which nucleic acid has to be transferred through the cell membrane into the target cell and released. We have performed extensive umbrella sampling simulations to obtain benchmark PMF profiles of four DNA/RNA nucleobase interactions with phospholipid bilayers using the AMBER and CHARMM force fields and a set of four different lipids. Based on these results, we are developing Martini parameters for these nucleobases and extending the simulations to larger systems including DNA/RNA strands. The results of this work will be useful in studies of DNA-binding proteins and lipoplexes, DNA-sequencing technology, the mechanism of viral protein RNA polymerase, and drug delivery systems.
1. Marrink et al., Chem. Soc. Rev. 42, 6801-6822, 2013.
2. Semple et al., Nature Biotech. 28, 172-U18, 2010.

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Lysolipid Concentration Effect on the Properties of a Membrane using Molecular Dynamics
J. David Orjuela[1], Chad Leidy[2], Günther H. Peters[3], Gilles P. Pieffet[4].
[1]Department of Physics, Universidad Nacional de Colombia, Bogota, Colombia, [2]Department of Physics, Universidad de Los Andes, Bogota, Colombia, [3]Department of Chemistry, MEMPHYS-Center for Biomembrane Physics, Technical University of Denmark, Lyngby, Denmark, [4]Department of Physics, Universidad Antonio Nariño, Bogota, Colombia.
Molecular dynamics simulations were performed to determine the free energy profile of the extraction process of a lysolipid molecule from a lipid bilayer. The simulations were done using DOPC membranes at different lysolipid concentrations to determine the effect of concentration on the extraction free energy profile. Calculations were performed using the Gromacs software package and the Umbrella Sampling technique. First a pulling simulation at constant rate was run in order to obtain the starting points for the posterior Umbrella Sampling simulations. These simulations were used to reconstruct the potential of mean force of the extraction process, where the reaction coordinate is the distance between the pulled lipid and the membrane.
The simulations allow us to determine the factors (e.g. interfacial interactions, enthalpic/entropic contributions) affecting the free energy profile and the force needed to extract a lysolipid molecule from the membrane, our aim being to understand how the presence of lysolipids changes the elastic properties of the membrane. Hydrolysis rates values measured experimentally with proteins such as PLA2 can provide a reference with which to compare the extraction free energies obtained from the potential of mean force. These results are relevant for understanding processes involving hydrolytic, interfacially active enzymes where lipids need to be extracted before the enzyme can perform its function.

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The Abundance of Ergosterol in Candida Species Does not Influence Fluconazole Sensitivity
Gayatri Suresh Kumar.
Chemistry and Biochemistry, University of Arkansas, Fayetteville, AR, USA.
Candidiasis an infection caused by the genus of yeast *Candida*. These commensal organisms are normally found on the skin and in the human body cavities; however, they can cause disease when the host defense or flora is disrupted or as a result of immunosuppression. Fluconazole is a favored antifungal drug to treat these infections. The fluconazole mode of action is to inhibit the cytochrome P450 enzyme 14 alpha-demethylase, thereby preventing the conversion of lanosterol to ergosterol, an essential component of fungal membranes. Unfortunately, some species of *Candida* are fluconazole-resistant. The goal of this work was to examine whether the cellular ergosterol content of various *Candida* species could be correlated with sensitivity to fluconazole. Initially, Minimum Inhibitory Concentration (MIC) assays were performed with *Candida* species to establish their sensitivity to the fluconazole. These data indicated that the majority were fluconazole-sensitive and a few species showed resistance, as expected. To establish whether there was a relationship between the ergosterol content and sensitivity to fluconazole, ergosterol and its precursor dehydroergosterol were extracted from various *Candida* species using a liquid-liquid organic extraction protocol. The level of each sterol was determined by UV spectroscopy, and expressed as a percentage of the wet weight of the cells. Our preliminary data indicates that the ergosterol content of the cells did not differ